

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- ☐ ☒ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
- ☐ ☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- ☐ ☒ The statistical test(s) used AND whether they are one- or two-sided
Only common tests should be described solely by name; describe more complex techniques in the Methods section.
- ☐ ☒ A description of all covariates tested
- ☐ ☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- ☐ ☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- ☐ ☒ For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
Give P values as exact values whenever suitable.
- ☒ ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- ☒ ☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- ☒ ☐ Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection

-RT-qPCR data collection was performed using CFX Maestro 1.1 version 4.1.2433.1219.
-Raw Nanostring targeted transcriptome profiling data was exported from the instrument into Nanostring nSolver v4.0 for QC. The data was exported to Microsoft Excel Office 365 v.16.01.13127.20266.
-LegendPlex data was collected with a FACS Canto II cytometer (BD Biosciences) using BD FACS Diva software (Version 10.6.1) and LegendPlex cloud-based software (Version 2020.05.14).
-Immunospot data was collected using Immunospot Professional v7.0.9.5
-ELISA data was collected using Biotek Cytation5 v.3.04.

Data analysis

-RT-qPCR analysis was performed using CFX Maestro 1.1 version v4.1.2433.1219.
-Nanostring data was analyzed using Nanostring nSolver Advanced Analysis 2.0 package to generate principal component analysis (PCA) figures and volcano plots, as well as to determine differential expression of transcripts compared to a pre-challenge baseline. Pathway analysis of this data was performed using Qiagen Ingenuity Pathway Analysis (IPA; Summer Release 2020). Network maps of differentially expressed mRNAs were imported into Metascape 3.5 and visualized using Cytoscape v3.8.0.
-LEGENDPlex data was analyzed using cloud-based LEGENDplex™ Data Analysis Software.
-Immunospot data was analyzed using Immunospot Professional v7.0.9.5
-ELISA data was analyzed by Biotek Cytation5 v.3.04. and Microsoft Excel Office 365 v.16.01.13127.20266.
-All statistical analysis was performed in Graphpad Prism v8.2.1.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

RNA reads data and statistics are provided as an extended data file (Source Data File 1). Other data that support the findings of this study are available from the corresponding author, T.W.G., upon reasonable request

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	As SARS-CoV-2 is a novel pathogen in humans, and prior studies in African green monkeys did not exist, animal group size was decided by the expected lethality (low to none, based the limited number of other COVID-19 studies in other species of non-human primates), and for ethical reasons, the minimum number of animals by which statistical inferences could be made (n=6 for antemortem data collected up to 5 dpi, n=3 for postmortem data collected 5 dpi, n=3 for ante- and postmortem data collected beyond 5 dpi).
Data exclusions	No data was excluded from the analysis.
Replication	Due to the ethical and technical challenges experiments involving animals, and specifically non-human primates in high-containment conditions, it was not feasible to conduct multiple experimental repetitions for this study. Representative photomicrographs were qualitatively considered to display lesions that were nominally or ordinaly measured by masking of the pathologist post-examination and ranking lesions to satiate the study objectives. Additionally, a thorough examination of multiple slides of the target tissues (e.g. 18 slides of lung) multiple times (up to 3 times per tissue) was performed in a timely manner to maintain interpretation consistency. Other data was collected from a single independent experiment with successful technical replication.
Randomization	Animals were issued a number from 1-6, and randomly assigned to groups using a random number generator.
Blinding	Blinding was not performed for this study, as it was not necessary to answer the questions set forth by the study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies
<input type="checkbox"/>	<input checked="" type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input type="checkbox"/>	<input checked="" type="checkbox"/> Animals and other organisms
<input checked="" type="checkbox"/>	<input type="checkbox"/> Human research participants
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Antibodies

Antibodies used	-Goat anti-Monkey IgG HRP pAb (Fitzgerald, Cat# 43R-IGO20-HRP, Lot# c15032720) -Monkey IgA alpha Antibody Peroxidase Conjugated (Rockland Immunochemicals, Cat # Cat: 617-103-006, Lot # 41791) -SARS Nucleocapsid Protein Antibody (Novus Biologicals, Cat # NB100-56683, Lot # 111003D-4) -Goat Anti-Rabbit IgG Antibody (H+L), Biotinylated (Vector Laboratories, Cat # BA-1000, Lot # ZG0122)
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Validation

-Anti-fibrin monoclonal mouse primary antibody (Sekisui Diagnostics, Cat # REF 350, Lot# 140714)
 -Goat Anti-Mouse IgG Antibody (H+L), Biotinylated (Vector Laboratories, Cat # BA-9200, Lot # ZB0324)

-Goat anti-Monkey IgG HRP pAb- The antibody has been validated by Western blot by the manufacturer. Data within this manuscript and PMID 32719371 validates its use for ELISA.
 -Monkey IgA alpha Antibody Peroxidase Conjugated- The antibody has been validated for ELISA by the manufacturer.
 -SARS Nucleocapsid Protein Antibody- The antibody has been validated for IHC-detection of SARS-CoV-2 nucleocapsid protein by the manufacturer and in this publication. Orthogonal strategies validation by vendor (Novus Biologicals): Dual RNAscope ISH-IHC: SARS Nucleocapsid Protein Antibody [NB100-56683] - Formalin-fixed paraffin-embedded tissue sections of SARS-CoV-2 infected human lung tissue were probed for SARS-CoV-2 viral RNA (ACD anti-sense specific probe v-nCoV2019-S [848561]); Fast Red chromogen, ACD [322360]). Adjacent tissue section was processed for immunohistochemistry using rabbit polyclonal anti-SARS Nucleocapsid Antibody [NB100-56683] at 15ug/mL with 1 hr incubation at 25 degrees Celsius followed by incubation with anti-rabbit IgG VisUCyte HRP Polymer Antibody [VC003] and DAB chromogen (yellow-brown). Tissue was counterstained with hematoxylin (blue). Specific staining was localized to SARS-CoV-2 infected cells.
 -Goat Anti-Rabbit IgG Antibody (H+L), Biotinylated- The antibody has been validated for IHC by the manufacturer.
 -Anti-fibrin monoclonal mouse primary antibody- The antibody has been validated for IHC by the manufacturer. This exact antibody is now offered by Biomedica Diagnostics (ref 350). For validation, this antibody was shown to successfully stain fibrin (beta chain of fibrinogen) in snap frozen human cardiac allografts. The antibody also successfully stained fibrin in formalin-fixed, paraffin embedded canine mammary neoplastic tissue and in formalin-fixed paraffin embedded rabbit pleural tissue (PMID: 1456881).
 -Goat Anti-Mouse IgG Antibody (H+L), Biotinylated- The antibody has been validated for IHC by the manufacturer.

Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)

Vero E6 (ATCC CRL-1586) was obtained from American Type Culture Collection (ATCC).

Authentication

Independent validation of the Vero E6 cell line was not performed outside of any authentication performed by ATCC.

Mycoplasma contamination

Cells were tested for mycoplasma contamination. No detectable mycoplasma or endotoxin levels were measured (< 0.5 endotoxin units (EU)/ml).

Commonly misidentified lines
(See [ICLAC](#) register)

No commonly misidentified cell lines were used in the study.

Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals

Research-naïve adult African green monkeys (*Chlorocebus aethiops*); 4 females, 2 males. The age of laboratory animals used in this study was not provided by the vendor.

Wild animals

No wild animals were used in the study.

Field-collected samples

No field-collected samples were used in the study.

Ethics oversight

The animal studies were performed at the Galveston National Laboratory, University of Texas Medical Branch at Galveston (UTMB) and were approved by the UTMB Institutional Animal Care and Use Committee. This facility is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

Note that full information on the approval of the study protocol must also be provided in the manuscript.